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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/585,721	08/08/2008	Jean-Francois Dubremetz	045636-5085	7202

9629 7590 01/20/2010

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EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
01/20/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,721	DUBREMETZ ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 6-9* is/are pending in the application.

4a) Of the above claim(s) *4 and 7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

1. This Office is responsive to Applicant's amendment and response filed 9-17-09. Claims 1, 4, and 6-9 are pending. Claims 1 and 6 are under examination. Claims 2-3 are cancelled. Claims 7-9 are new. Claims 4 and 7-9 are withdrawn from consideration.

Election/Restriction

2. Newly submitted claims 7-9 and amended claim 4 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Original claims filed on 7/12/2006 are drawn to a product. Amended claims filed on 9/17/2009 are drawn to a method and product. Applicant has constructively elected invention on 7/12/2006 drawn to a product.

The action on the merits on 4/17/2009 of the instant application has been examined.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 4 and 7-9 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Grounds of Priority Maintained

3. Acknowledgment is made of applicant's claim for foreign priority based on application filed on 7/12/2006. It is noted, however, that applicant has not filed a certified copy of the application as required by 35 U.S.C. 119(b).

Objections/Rejections Withdrawn

4. In view of the Applicant's amendments and remarks the following objections/rejections are withdrawn.

a) Objection to the specification for the use of trademarks is withdrawn in light of applicant's amendment to the specification.

b) Rejection to claims 4-5 under 35 U.S.C. 101 because the claimed invention was not supported by a well established utility is withdrawn in light of applicants cancellation of claim 5 and in light of applicant's amendment thereto to claim 4.

c) Rejection of claims 1-5 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of applicants cancellation of claims 2-3 and 5 and in light of applicant's amendment thereto to claims 1 and 4.

d) The rejection of claim 1 under 35 U.S.C. 103(a) as being unpatentable over Bassuny et al 2003 Infection and Immunity Vol. 71 No. 11 pgs.6222-6228 and Meissner et al 2002 Journal of Cell Science 115 pgs. 563-574.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The rejection of claim 6 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement are maintained for the reasons set forth in the previous office action. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant arguments:

Applicants arguments filed in response to the 35 U.S.C. 112, first paragraph, September 17, 2009 is carefully considered, but not found to be persuasive for the reasons below.

A) Applicants state that the present application does show a challenge experiment which demonstrates protection against infection and that Example 4, on page 23, lines 25 to 28, discloses that "21 mice (batch 2) received the micl-3KO mutant and were then reinfected approximately 1 month later with cystogenic Toxoplasma gondii strain 76." Applicants state the immunization step is the administration of micl-3 KO mutant and the challenge step is the latter infection with Toxoplasma gondii strain 76K and the mice immunized with the mic1-3KO mutant formed virtually no brain cysts during the re-infection with the Toxoplasma gondii strain 76K (see page 26, lines 8-15). Applicants argue that in the challenge experiments, the protective

effect noticed after the administration of the mic1-3KO mutant strain demonstrates that a Toxoplasma gondii strain comprising inactivated adhesins MIC 1 and MIC3 elicits a protective immune response against a latter Toxoplasma gondii infection.

B) Applicants state the experiments that were performed on ewes consisted of i) immunizing two batches of ewes, one of these batches with a low dose and the other batch with a high dose of micl-3KO tachyzoites and ii) infecting the gestating ewes by feeding them with 400 oocysts of Toxoplasma gondii (see Example 5 on page 28, lines 10 to 12 and page 30, lines 19 to 24) which shows the reduction of febrile abortions (abortions which occur following the thermal peak following the infection) caused by Toxoplasma gondii through the administration of mic1-3 KO mutant strain and demonstrates that the administration of mic1-3KO mutant strain also reduces the rate of abortions due to the infection of the fetus with Toxoplasma gondii (see Table II on page 33 and Table V on page 37). Applicants argue that in both of these challenge experiments, the protective effect noticed after the administration of the mic1-3KO mutant strain demonstrates that a Toxoplasma gondii strain comprising inactivated adhesins MIC 1 and MIC3 elicits a protective immune response against a latter Toxoplasma gondii infection. Applicants respectfully point out that Table VI, on page 37 of the application, which summarizes the results obtained with gestating ewes vaccinated with a mic1-3KO mutant strain, indicates that vaccination with mic1-KO mutant strain, named ToxoKO in Table VI, induces a protection of 66.6% and this level of protection is similar to the level of protection conferred by administration of Toxoplasma gondii S48 strain, which is the Toxoplasma gondii strain used in the only anti-toxoplasmosis vaccine commercially available (TOXOVAX®). Applicants also point out that there is zero protection only with the control batch of 12 ewes, i.e. the ewes which are not immunized before being challenged with Toxoplasma gondii.

Examiner's Response to Applicant's Arguments:

In response to applicant's statement in (A) as set forth supra, Although the specification discloses micl-3KO mutant and the challenge step of mice immunized with the mic1-3KO mutant and the re-infection with the Toxoplasma gondii strain 76K which formed virtually no brain cysts (see page 26, lines 8-15). The claims are broadly drawn to a vaccine comprising any mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by any mutation of each of MIC1 and MIC3 genes. Therefore the claims reciting "a mutation in

of each of MIC1 and MIC3 genes" can be any number of mutations that can be created to be an open ended number of mutations. The data as set forth supra demonstrate that the vaccine composition confers "protection" using micl-3KO against infection by Toxoplasma gondii strain 76K but does not demonstrate protection against all Toxoplasma gondii strains utilizing a given mutant strain of *Toxoplasma gondii*. Therefore the rejection is maintained.

In response to applicant's statement in (B) as set forth supra, the results on Tables 1-Table VI, on pages 33-37, summarizes the results female ewes were infected with oocysts of Prugniaud strain (PRU) at mid-gestation which show no febrile abortions occurred from ewes vaccinated with a mic1-3KO mutant strain, however the data disclosed in Tables II and V display the results of infectious abortions (see pg. 34 Table III and Table V pg. 37). Moreover, the specification states "that febrile abortions are abortions that are occur subsequently (at a later time) to a thermal peak which follows infection" (see pg. 32 line 35). Hence, the data as set forth supra demonstrate the reduction of febrile abortions due to the results of infectious abortions and the statement disclosed in the specification aforementioned above. Therefore, the specification is only limited to the reduction of febrile abortions caused by *Toxoplasma gondii* through the administration of the mic1-3KO mutant, consequently, the data as set forth supra does not demonstrate that the composition confers "protection" against infection by Toxoplasma gondii. Therefore the rejections are maintained.

As outlined previously, while being enabling for the reduction of febrile abortions caused by *T. gondii* through the administration of the mic1-3KO mutant does not provide enablement for any vaccine comprising any mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by any mutation of each of MIC1 and MIC3 genes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

(A) The nature of the invention;

(B) The breadth of the claims;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention: The claims are drawn to a vaccine comprising a mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by a mutation of each of MIC1 and MIC3 genes.

Breadth of the claims: The instant claims encompass protection against any of Toxoplasma gondii strain with a vaccine comprising a mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by any mutation of each of MIC1 and MIC3 genes.

Guidance of the specification/The existence of working examples: The specification discloses, mice immunized with a mutant, wherein MIC1 and MIC3 were inactivated (mic1-3KO mutant) (see pg. 12 and Example 4). The specification discloses the mice form virtually no brain cyst during a reinfection with the Toxoplasma gondii strain 76K with a 99.9% protection. Therefore the data as set forth supra demonstrate that the vaccine composition confers "protection" using micl-3KO against infection by Toxoplasma gondii strain 76K but does not demonstrate protection against all Toxoplasma gondii strains. The specification discloses ewes immunized with mic1-3KO (see pgs. 28-30) and infected with oocysts of PRU strain at mid-gestation (see pg. 30 lines 20-30). Moreover, the specification discloses Tables 1-Table VI, on pages 33-37, which summarizes the results female ewes infected with oocysts of Prugniaud strain (PRU) at mid-gestation which show no febrile abortions occurred from ewes vaccinated with a mic1-3KO mutant strain, however the data disclosed in Tables II and V display the results of infectious abortions (see pg. 34 Table III and Table V pg. 37). Moreover, the specification states "that febrile abortions are abortions that are occur subsequently (at a later time) to a thermal peak which follows infection" (see pg. 32 line 35). Hence, the data as set forth supra demonstrate the

reduction of febrile abortions due to the results of infectious abortions and the statement disclosed in the specification aforementioned above. Therefore, the specification is only limited to the reduction of febrile abortions caused by *Toxoplasma gondii* through the administration of the mic1-3KO mutant. Therefore the data as set forth supra does not demonstrate that the composition confers "protection" against infection by Toxoplasma gondii. Moreover, there is no data regarding the induction of a protective immune response to a given pathogen was disclosed.

The data merely shows that said composition reduces the number of mice and ewes dying from Toxoplasma gondii. Furthermore the specification discloses data only for Toxoplasma gondii strain. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model. The working examples do not disclose any empirical data or results indicative of a vaccine comprising a mutant strain as claimed against infection by all Toxoplasma gondii strains.

The specification does not disclose any working example that the recited vaccine as claimed will work against infection by all Toxoplasma gondii strains with mic1-3KO. A vaccine by definition must provide protection against an infection demonstrable by challenge experiments. The specification is devoid of any teaching that the claimed vaccine against infection caused by any strain of Toxoplasma gondii discloses a protective response against any subject.

State of the art: Although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from infection (Chandrashekar et al., US Patent 6,248,329, col. 1, lines 35-41). It is well recognized in the vaccine art, that it is unclear whether an antigen derived from a pathogen will elicit protective immunity. Ellis (Chapter 29 of Vaccines, Plotkin, et al. (eds) WB Saunders, Philadelphia, 1998, especially p. 571, paragraph 2) exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.., and thus protect the host against attack by the pathogen." Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and

function cannot be predicted. For the reasons set forth supra, the state of the art is has limitations to a vaccine composition and the state of the art is unpredictable with regard to the recited vaccine as claimed.

In conclusion, the claimed invention is not enabled for any vaccine comprising any mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by any mutation of each of MIC1 and MIC3 genes. The instant claims encompass protection against any of Toxoplasma gondii strain with a vaccine comprising a mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by any mutation of each of MIC1 and MIC3 genes. The state of the art teaches that there are limitations to the recited vaccine composition and the state of the art is unpredictable. In view of the lack of support in the art and specification for an effective vaccine, it would require undue experimentation on the part of the skilled artisan to make and use the vaccine as claimed; therefore the claims are not enabled. The specification is devoid of any teaching that the claimed vaccine against infection caused by any strain of Toxoplasma gondii discloses a protective response against any subject. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed method.

New Grounds of Rejections

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meissner et al 2002 Journal of Cell Science 115 pgs. 563-574.

The claim is drawn to a mutant strain of Toxoplasma gondii in which adhesion MIC1 and adhesion MIC3 are inactivated by any mutation of each of MIC1 and MIC3 genes.

Meissner et al teach a mutant strain mic1ko of Toxoplasma gondii (see 569 column 1 second paragraph and Figure 6) which correlates to a mutant strain comprising a mutation which inactivates the adhesin MIC1. Meissner et al teach Toxoplasma gondii microneme protein 3 (TgMIC3) as a soluble adhesin (see pg. 573 column 2 paragraph 1) and is capable of binding host cells (see pg. 571 column 2) and is similar to MIC1 in function.

Meissner et al teach does not teach a mutant strain of Toxoplasma gondii in which adhesion MIC3 is inactivated by any mutation of a MIC3 gene.

It would have been prima facie obvious at the time the invention was made to inactivate the MIC3 gene because the MIC3 gene is a major soluble adhesive protein (see pg. 573 column 2 paragraph 1) leading to host cell attachment and invasion and hence makes a good target for vaccine/treatment modalities. Moreover, one would be motivated to create a strain containing multiple mutations in order to reduce the possibility of wild-type reversion.

One would have a reasonable expectation of success because said the creation of double mutants is well known in the art.

Conclusion

7. No claims are allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina A Archie
Examiner
GAU 1645
REM 3B31

/Robert A. Zeman/
for Nina Archie, Examiner of Art Unit 1645